Dr A Haragan (1,2), Prof JR Gosney (1,2), Dr Garcia-Finana (2), Prof JK Field (2), Dr M Davies (2), Dr C Escriu (3) and Dr A Gruver (4).

Royal Liverpool University Hospital, UK(1); University of Liverpool, UK(2); Clatterbridge Cancer Centre, UK(3); Eli Lilly, US(4).

Digital Core Needle-Biopsy to Assess PD-L1 Expression in Non-Small Cell Lung Cancer: Optimal Sampling and Need for Re-Biopsy

Background

Assessing expression of PD-L1 on tumour cell membranes by immunochemistry is an important complementary or crucial companion diagnostic test to guide the use of immune modulating checkpoint inhibitors in the treatment of non-small cell lung cancer (NSCLC).[1] Unfortunately, the known temporal and spatial heterogeneity of PD-L1 expression raises the important question of how to ensure that the small biopsy specimens with which this assessment is usually made are adequately representative of PD-L1 expression by the whole tumour.[2]

Method

Expression of PD-L1 was assessed in sections of 65 tissue blocks from 20 primary pulmonary adenocarcinomas and 20 primary pulmonary squamous cell carcinomas using the Ventana SP263 antibody and a validated protocol. Scoring was performed by two appropriately-trained pathologists with extensive experience in its interpretation. After conventional assessment, slides were digitally scanned and divided into squares of 1mm² area to form a digital database (mean of 150 data-points per tumour), which were assigned co-ordinates and re-scored. By these means, multiple, "digital core biopsies" (Figure 1) approximating a 17 gauge needle were simulated in sequential fashion, and expression in these was compared to that in the whole tumour and categorised by current UK prescribing guidelines*

Results

PD-L1 score (%)	**Total number of cases**	**Cases where PD-L1% from single DCBx changed scoring category vs whole tumour***	**Cases where PD-L1% from two DCBx changed scoring category vs whole tumour***	**Cases where PD-L1% from three DCBx changed scoring category vs whole tumour***	**Cases where PD-L1% from four DCBx changed scoring category vs whole tumour***	**Cases where PD-L1% from five DCBx changed scoring category vs whole tumour***	**Focal expression primary pattern in non-correlative cases**
<1	14	2	2	6	2	**2**	**Y**
1-10	13	6	1	5	1	**0**	**Y**
11-49	10	1	0	1	0	**0**	**Y**
50-100	13	0	0	0	0	**0**	**n/a**
All	**50**	**18%**	**6%**	**3%**	**0.75%**	**2 (4%)**	

PD-L1, programmed death ligand 1; DCBx, Digital Core Biopsy
***Based on pembrolizumab categories as: 1st line ≥50%, 2nd line 1-49%; nivolumab categories as: ≥1% (for adenocarcinoma)**

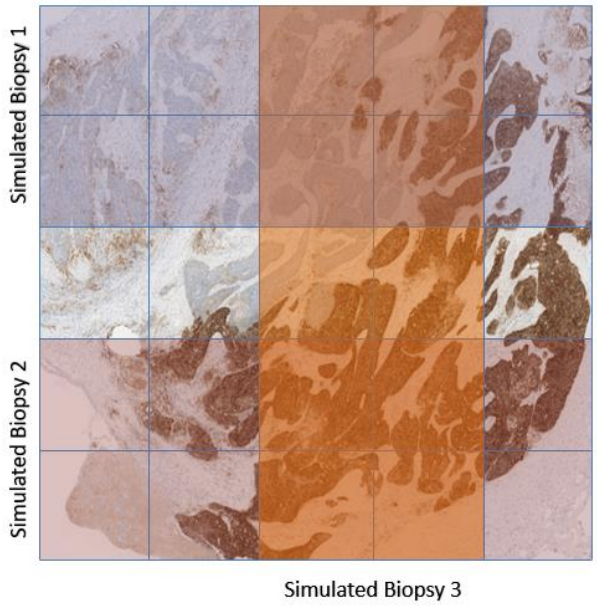

Fig 1. NSCLC overlaid with 1mm² grid and examples of "digital biopsies"

3 separate "digital biopsies" (these simulate half a 17G core)from a small area of tumour which illustrates how position of biopsy even in a 2D space can potentially change PD-L1 TPS %. This error is notably increased with focal positivity and low PD-L1 TPS tumours.

Conclusion

In the majority of cases, three digital core biopsies achieved closest correlation with the whole tumour, with little greater accuracy achieved by assessing four cores or more. Correlation was weakest when expression was low and very focal, an important consideration in view of the importance of the '1% cut-off' used commonly to guide immune checkpoint therapy.[3] Using this model as a guide, a single good quality biopsy (2x10mm² area) is sufficient for most tumours scoring 11% or greater PD-L1 expression. However, in the lower range of expression, re-biopsy might be routinely considered if there is doubt about specimen adequacy.

References

1. **Büttner *et al*.: Programmed Death-Ligand 1 Immunohistochemistry Testing: A Review of Analytical Assays and Clinical Implementation in Non-Small-Cell Lung Cancer. J Clin Oncol. 2017 Dec 1;35(34):3867-3876**

2. **Ilie *et al*.: Comparative study of the PD-L1 status between surgically resected specimens and matched biopsies of NSCLC patients reveal major discordances: a potential issue for anti-PD-L1 therapeutic strategies. Ann Oncol. 2016 Jan;27(1):147-53.**

3. **Hisrch *et al*.: PD-L1 Immunohistochemistry Assays for Lung Cancer: Results from Phase 1 of the Blueprint PD-L1 IHC Assay Comparison Project J Thorac Oncol. 2017 Feb;12(2):208-222.**